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HORMONE
RESEARCH

Horm Res 2008;70:59–64
DOI: 10.1159/000129680

Received: August 15, 2007
Accepted: October 17, 2007
Published online: May 21, 2008

Long-Term Non-Surgical Therapy of Severe Persistent Congenital Hyperinsulinism with Glucagon

K. Mohnike[a] O. Blankenstein[b] A. Pfuetzner[c] S. Pötzsch[a] E. Schober[d]
S. Steiner[c] O.T. Hardy[e] A. Grimberg[e] W.M. van Waarde[f]

[a]Department of Pediatrics, Otto von Guericke University of Magdeburg and [b]Charité University of Medicine, Berlin, Germany; [c]Pharmaceutical Discovery Corp., Elmsford, New York, N.Y., USA; [d]Department Pediatrics, University of Vienna, Austria; [e]Division of Pediatric Endocrinology, The Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, Pa., USA, and [f]Department of Pediatric Endocrinology, University Hospital of Groningen, The Netherlands

Established Facts

- In diazoxide-resistant congenital hyperinsulinism, high rates of glucose via a central catheter and intravenous infusions of glucagon are recommended to stabilize euglycemia.
- The rationale of glucagon therapy comes from the observation of increased liver glycogen content due to insulin-dependent inhibition of glycogenolysis.

Novel Insights

- A continuous subcutaneous infusion of glucagon with or without octreotide-stabilized euglycemia over months and years without the need of a central catheter.

Key Words
Congenital hyperinsulinism · Continuous subcutaneous glucagon infusion · Diazoxide-resistant congenital hyperinsulinism · Hypoglycemic episodes · Octreotide and subcutaneous glucagon infusion · Severe persistent congenital hyperinsulinism

Abstract

Background: Congenital hyperinsulinism (CHI) is characterized by severe hypoglycemia caused by dysregulated insulin secretion. The long-term outcome is dependent on prevention of hypoglycemic episodes to avoid the high risk of permanent brain damage. Severe cases are usually resistant to diazoxide or nifedipine. In addition, somatostatin analogues are ineffective in a subgroup of patients to achieve stable euglycemia. In these infants the only remaining long-term option has been subtotal pancreatectomy with high risk of diabetes mellitus. Intravenous infusions of glucagon are used as immediate treatment to stabilize euglycemia in affected newborns. The rationale of this treatment comes from the observation of an increased glycogen content of the liver when glycogenolysis is inhibited by insulin. ***Objective:*** To review the efficacy and safety of long-term subcutaneous

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0301–0163/08/0701–0059$24.50/0

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Dr. Klaus L. Mohnike
Department of Pediatrics, Otto von Guericke University
Leipziger Strasse 44, DE–39120 Magdeburg (Germany)
Tel. +49 391 67 24031, Fax +49 391 67 290038
E-Mail susann.empting@med.ovgu.de

glucagon infusion as a potential therapeutic option for blood glucose stabilization in infants with severe CHI without the need of additional intravenous glucose or immediate surgical intervention. ***Method:*** Retrospective review of 9 children with CHI who received continuous subcutaneous infusion of glucagon for weeks or months. Glucagon was added to octreotide to replace octreotide-induced suppression of endogenous glucagon secretion, thereby liberating glucose by stimulation of hepatic glycogenolysis. In 3 cases, a stabilized formulation of glucagon was used to prevent glucagon crystallization that frequently occurs in smaller volumes. ***Results:*** Introduction of glucagon allowed the reduction or discontinuation of central glucose infusion in all children studied. In 2 patients, glucagon was introduced due to recurrent hypoglycemia despite subtotal pancreatectomy. Six out of 9 children were discharged home on this treatment, which their parents were able to continue without further symptomatic hypoglycemia, convulsions or unconsciousness. In 3 children, subcutaneous glucagon was continuously administered for 1–4 years leading to stable euglycemia. However, 2 children with diffuse type still required subtotal pancreatectomy. As a possible side effect, 2 children developed erythema necrolyticum, which resolved after discontinuation of the glucagon infusion. This has been described before in glucagonoma. ***Conclusion:*** In this retrospective series, combination therapy of low-dose octreotide and subcutaneous glucagon infusion has been effective in preventing hypoglycemic episodes in severe CHI. We propose this may serve as a therapeutic option in place of high rates of glucose infusion through a central venous catheter and as an alternative to subtotal pancreatectomy in diffuse type of CHI.

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Introduction

Congenital hyperinsulinism (CHI) is characterized by severe hypoglycemia due to dysregulated insulin secretion. The long-term outcome of infants with persistent hyperinsulinemic hypoglycemia depends on the prevention of hypoglycemic episodes to avoid the high risk of permanent brain damage [1–7]. Most patients with neonatal-onset CHI have mutations of the sulfonylurea receptor *(SUR1)*, a component of the β-cell ATP-sensitive potassium channel (ABCC8), and require intensive care either surgically or medically [2, 5, 8, 9]. *SUR1* mutations can occur as an autosomal recessive trait, leading to diffuse CHI that impairs function of all β cells, or as focal adenomatosis, in which loss of heterozygosity results in reduction to homozygosity for a paternally inherited mutated *SUR1* allele.

For the nearly 50% of patients with the focal form of CHI, surgical excision of the focal lesion leads to permanent cure [2, 10]. To differentiate focal from diffuse CHI, ^{18}F-DOPA-PET (or integrated PET/CT) is the preferred method [11]. In diffuse CHI, more extensive subtotal pancreatectomy is frequently performed, with higher rates of complications and less likelihood of cure. Apart from surgical intervention, treatment modalities for CHI include high glucose infusion rates, continuous gastrostomy feeds and use of medications. High concentration glucose infusion by central venous catheter has been used to maintain euglycemia for periods up to several weeks [12]. Often, oral feeding is difficult or even impossible in these children [2, 13–15]. Alternatively continuous tube feeding with high carbohydrate content has been used. Spontaneous remission occurs, sometimes within weeks and in other cases after several years [1, 2, 14, 16].

A number of drugs are currently used in stabilizing euglycemia. Diazoxide was introduced in 1965 as a treatment for a subgroup of CHI patients [17]. Diazoxide acts on the sulfonylurea receptor, which limits its action in cases with SUR mutations [2, 9]. Other drugs, e.g. octreotide [14, 18] or calcium channel blockers [19, 20], reduce insulin secretion without involving the sulfonylurea receptor [2, 9]. In addition to drugs whose effect is to inhibit insulin secretion by pancreatic β cells, intravenous glucagon infusion has been used to increase blood glucose levels by stimulation of hepatic glycogenolysis. The rationale of this treatment comes from the observation of an increased glycogen content of the liver when glycogenolysis is inhibited by the inappropriately high insulin levels [21–23]. Furthermore in a recent study in children with different types of hypoglycemia, a diminished glucagon serum concentration during hypoglycemia has been demonstrated specifically in CHI [24].

Here we report on continuous subcutaneous glucagon infusion as a therapeutic option, with or without concomitant octreotide: (1) to stabilize euglycemia for weeks without the need of high glucose infusion by a central catheter; (2) to avoid pancreatectomy or re-operation in patients with diffuse type of CHI, and (3) to improve the stability of glucagon in aqueous solution in a subgroup of 3 patients a stabilized glucagon preparation was used.

Table 1. Clinical description of patients

	No operation			Glucagon after operation		Preoperative glucagon			
Patient	1	2	3	4	5	6	Tec 1	Tec 2	Tec 3
Gender	F	F	M	F	M	M	M	F	F
Histologic type; age at pancreatic surgery	No surgery	No surgery	No surgery	Diffuse 3 weeks	Diffuse, repeated pancreatic operations at age 33 and 88 days, 2.5 years	Diffuse	Focal 4 months	Diffuse 5 months	Focal 6.5 months
Mutation in ABCC8 (SUR1)	Not tested	Not tested	R1437Q paternal allele only	1672-9T>A/ 2698-2A>G	DelF 1388/3992-9 G>A	4481 G>A paternal allele only	One allele D1471N	50T>C/ 2394-1G>A	Not tested
Gestation age, weeks	40	Full term	40	37	Information not available	38	40	40	30
Birth weight, g	4,280	Information not available	3,110	3,820	3,544	3,955	3,600	4,800	1,870
Age of initial hypoglycemia, h	36	Seizures at 2 months of age	24	4	72	Birth	24	6	18
Presenting blood glucose, mmol/l	1.1	1.5	1.3	0.9	1.1	1.3	0.5	0.8	0.8
Insulin at hypoglycemia, mU/l	26.0	8.8	5.6	218.0	Information not available	50.0	19.0	419.0	14.5
Glucose infusion rate, mg/kg/min	16.0	7.0	20.0	14.0	Information not available	14.0	20.0	26.0	14.0
Maximum dose of octreotide, μg/kg/day	15	10	15	None	20	8	35	10	30
Age at start; maximum dose of s.c. glucagon, mg/kg/day	46 days; 0.026	5.5 months; 0.24	165 days; 0.8	120 days; 0.4	0.1	43 days; 0.41	27 days; 0.25	42 days; 0.26	112 days; 0.46
Discharge from hospital with glucagon	8 weeks	Transferred to local hospital on combination therapy and then home	25 weeks	10 weeks	3 months	No	8 weeks	No	No
Blood glucose <2.6 mmol/l during s.c. glucagon	None	None	None	None		Information not available	<3 times/ month	5 times/ month	None
Duration of glucagon treatment	4 years	>4 months	6 weeks	1.3 years	2 years	10 days	2.5 months	3.5 months	Days
Age at last presentation	5 years	9.5 months	8 months	1.5 years	10 years	6.5 months	7 years	6 years	2 years
Erythema necrolyticum	No	No	No	No	No	No	No	Yes	Yes

Tec = Glucagon-Technosphere™.

Methods and Results

Nine children with neonatal-onset CHI from Germany, The Netherlands, Austria and the Children's Hospital of Philadelphia (USA) were treated initially with glucose infusions via a central catheter (table 1). Diazoxide was administered in doses of 10–15 mg/kg/day as first-line medical therapy, but shown to be ineffective in stabilizing blood glucose after 10–20 days. Second, octreotide was given in doses of 15–60 μg/kg/day by intermittent subcutaneous injections without establishing stable euglycemia. An intravenous infusion of 1–3 mg/day glucagon was then initiated, and shown to be effective when the central glucose infusion was reduced or discontinued. Two children were found to have focal CHI, but surgery was delayed for technical reasons. In the remaining patients with diffuse type CHI, stable euglycemia was not achievable with oral feeding and subtotal pancreatectomy was therefore recommended. The parents of patient 1 refused pancreatectomy, and in 2 (patients 4 and 5) recurrent hypoglycemia persisted after subtotal pancreatectomy. To avoid subtotal pancreatectomy or re-operation, subcutaneous glucagon was considered as an alternative therapeutic approach. Emergent approval for combination octreotide/glucagon infusion via portable subcutaneous pump was obtained from the Institutional Review Board of the Children's Hospital of Philadelphia. Continuous subcutaneous infusion of glucagon via an infusion pump was started at this time, at doses of 0.026–0.8 mg/kg/day. It was used in combination with octreotide in 8 of the 9 patients. A mean dose of 15 μg octreotide/kg/day (range 0–35) was used.

In all children, central glucose infusion was reduced or discontinued after introduction of glucagon. Six children were discharged home and their parents were able to continue treatment without further symptomatic hypoglycemia, convulsions or unconsciousness. In 2 children this treatment was introduced due to recurrent hypoglycemia after subtotal pancreatectomy. One patient with focal type was successfully operated by partial pancreatectomy. In 3 patients, subcutaneous glucagon was continuously administered for 1–4 years leading to stable euglycemia. One of these patients developed recurrent hypoglycemia at age 2.5 years and a third pancreas operation was performed.

In 3 out of 9 patients (patient 6, Tec 2 and Tec 3) we were not able to discharge home, 1 with focal type (Tec 3) was successfully operated by partial pancreatectomy.

Glucagon infusion was complicated by frequent catheter obstruction, occurring daily or 2–3 times weekly. In 1 case this led to the decision of subtotal pancreatectomy (patient 6), but in the others, parents were able to overcome these catheter obstructions in order to avoid pancreatectomy. To overcome this technical problem a new formulation of glucagon-Technosphere™ was developed and approved by the Ethics Committee of the Otto von Guericke University, Magdeburg. Administration of glucagon-Technosphere™ in 3 children resulted in stabilized blood glucose with only few hypoglycemic episodes. Less then 3 alarm warnings per week alerted the parents but were surpassed spontaneously or after changing the infusion system.

Regarding outcome, a healthy psychomotoric and physical development has been reported at the last visit in 8 of the children (age 6 months to 10 years), while 1 (patient 5) developed seizure disorder and visual impairment. In 2 children (patients 8 and 9) erythema necrolyticum occurred but resolved without scarring after glucagon was stopped [25].

Discussion

The main goal of CHI treatment is the avoidance of hypoglycemia-induced brain damage. Treatment includes a regimen of medical and surgical options [1–3, 5, 26, 27].

Diazoxide is the first drug of choice in CHI with an effective dose up to 15 mg/kg/day [2, 7]. It binds to SUR1 thereby inhibiting the closure of this ion channel and thus preventing depolarization, calcium influx and lastly insulin release [7, 9, 28]. The neonatal-onset type of CHI is often due to a mutation of the SUR, as has been shown in 6 of our patients. Diazoxide is sufficient to maintain euglycemia in children with types of CHI limited to a defect upstream of the SUR, such as mutations in the genes encoding the glucokinase enzyme, or glutamate dehydrogenase (hyperinsulinism-hyperammonemia syndrome) but a subgroup of patients with dominant mutations of SUR may also respond [29, 30]. Exceptionally, some patients with recessive mutations have been described as diazoxide-responsive [31].

In the diazoxide-resistant type of CHI, inhibition of insulin secretion by a mechanism downstream to this receptor [21, 32, 33] has been an option. Until now, therapeutic recommendations in diazoxide-resistant CHI have been limited to octreotide, calcium channel blockers and intravenous infusions of glucagon [12, 33]. Blocking calcium influx by the use of calcium channel blockers has been used with conflicting results and with only limited success in severe neonatal-onset CHI [20, 33].

In 1993, Glaser et al. [14] and Thornton et al. [18] reported on the administration of octreotide subcutaneously in CHI for up to 4–5 years. Octreotide does not entirely eliminate hypoglycemic events [12], which recur even with increasing doses [18]. Various side effects have been seen when octreotide has been used in a number of different pathological situations, usually at higher doses (20–40 μg octreotide/kg/day) [18, 34]. Gallbladder calculi have been reported in 3/20 adolescents treated for tall stature with octreotide [34]. General side effects with gastric atony, nausea, diarrhea and abdominal discomfort were reported by a minority of subjects, including 2 of our patients [35]. In our patients, growth and weight were not influenced by the applied dose of octreotide (mean 15 μg/kg/day).

In this observational study, a combination of octreotide and subcutaneous glucagon infusions was tried as an alternative approach to eliminate entirely the hypoglycemic events seen when octreotide alone is used for CHI. Glucagon has been used for the immediate treatment of hypoglycemia in patients with diabetes mellitus who injected overdoses of insulin. Several papers reported on the use of glucagon in CHI [2, 13, 22, 23, 36, 37]. Its action on hepatic glycogen storage has long been known. Administration of 0.1 mg/kg glucagon in an infant with CHI increased hepatic glycogenolysis and caused an increase of glucose production from 4 to 10 mg/kg/min [21].

Our first goal was to stabilize euglycemia for weeks without the need of high glucose infusion by a central catheter. A reduced daily dose of 8–15 μg octreotide/kg was used in 5 children which is considerably lower compared to doses used with octreotide alone. In patient 4, glucagon alone was administered for 15 months leading to stable euglycemia. In all children, central glucose infusion was reduced or discontinued after introduction of glucagon. In 3 out of 6 children, subcutaneous glucagon was successfully administered continuously for 1–4 years without further symptomatic hypoglycemia, convulsions or unconsciousness.

Our second goal, to avoid pancreatectomy or re-operation in diffuse CHI, was reached in 5 children (patients 1–5) by continuous subcutaneous infusion of glucagon with or without octreotide. Subtotal pancreatectomy was decided in 2 children, in 1 due to erythema necrolyticum due to glucagon administration (patient 9) and in the other (patient 6) due to technical problems with catheter obstructions following glucagon crystallization.

Because glucagon is a very labile molecule in aqueous solution, it crystallizes out of the solution over time which can result in blockage of the infusion apparatus. This became particularly problematic as the doses, and hence glucagon concentration, increased. In 3 patients we used a new formulation of glucagon which is pH-sensitive, being a solid at a pH <5.8 and soluble at pH ≥ 6.5. Technosphere™ is a proprietary diketopiperazine molecule of which a hydrogen group binds to the glucagon molecule, thereby stabilizing it from degradation in aqueous media, forming solid spheres of about 2 μm in size. An aqueous suspension of the formulation in sterile saline has the appearance of milk. Since the particles are less than one third of a red blood cell in diameter and have an absolute density close to one, they readily remain suspended and can be administered without obstructing the catheter. The subcutaneous tissue raises the pH level to neutral and the spheres dissolve, releasing the intact glucagon. Technosphere™ has been used to stabilize other protein hormones [38–40]. At present we have only limited experience with Technosphere™-stabilized glucagon infusion due to its restricted availability. Further clinical trials are needed before its use may be advocated.

As possible side effects of glucagon treatment, erythema necrolyticum migrans has been described before in 2 of our patients [25]. This occurred during both intravenous and subcutaneous glucagon administration, but disappeared after discontinuation of the drug. It is unclear whether the induction of erythema necrolyticum migrans is dose-dependent, but increased bioavailability of glucagon due to Technosphere™ stabilization might be taken into consideration.

In conclusion, a combined therapy of low-dose octreotide and a stabilized subcutaneous infusion of glucagon may be a useful treatment for CHI under at least three different circumstances. First, it can reduce the amount of intravenous glucose needed to stabilize blood glucose levels during the diagnostic period, thereby decreasing the risk of high volume and high osmotic complications until surgical treatment can be performed for either focal or diffuse type of CHI [7, 10]. Second, it may serve as an additional option in the long-term management of diffuse CHI, instead of near-total pancreatectomy, thereby preventing possible failure of the exocrine pancreatic function and the later development of diabetes mellitus. Finally, for challenging patients with recurrent hypoglycemia after near-total pancreatectomy, glucagon infusion may provide long-term stabilization.

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